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ALLEN, M EXAMINER

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ART UNIT	PAPER NUMBER
1812	12

DATE MAILED: 09/19/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on election 7/10/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 38-54, 57-70 are pending in the application.
   Of the above, claims 38-54 are withdrawn from consideration.
2. ☒ Claims 1-37, 55-56 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 57-70 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 38-54, 57-70 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Applicant's election without traverse of Group I, claims 1-37 and 55-56, in Paper No. 10 is acknowledged.

Claims 38-54 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 10.

In the preliminary amendment filed 07 August 1995, applicant cancelled claims 1-37 and 55-56 and added new claims 79-92. The original claims were numbered 1-56. No claims 57-78 have been presented previously in this application. As such, new claims 79-92 have been renumbered as 57-70 in keeping with 37 CFR 1.126. The dependencies of these claims have been corrected as well.

Claims 57-70 are under consideration by the Examiner.

Applicant is encouraged to file an information disclosure statement.

The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed alterations have been made to the oath or declaration (see 37 C.F.R. §§ 1.52(c) and 1.57). (See inventor Irving.)

Claim 70 is objected to as being duplicative of claim 69. Each of these claims appears to possess the same limitations. Clarification is requested.

Claims 57-70 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to chimeric proteins as set forth below. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The functional language of claim 57 "membrane bound protein initiates signalling in said host cell" is inaccurate. The membrane bound protein will actually initiate a signal only when the appropriate ligand is bound or some other appropriate signal (e.g. receptor aggregation) is received by the receptor (depending on the nature of the receptor) not merely when the DNA encoding it is expressed.

Claim 57 recites "resulting in activation of a messenger system." The specification describes second messenger systems. (See page 7 of the specification.) The specification does not appear to describe the metes and bounds of what other messenger systems would be encompassed. No other messenger systems appear to be described.

The claims are directed to chimeric proteins that will initiate signaling in a host cell after expression of the DNA encoding them and an appropriate signal is received by the chimeric protein as set forth above. The chimeric proteins contain a transmembrane domain and therefore will be membrane bound. The specification does not set tell how to use any chimeric protein that does not initiate signaling in a host cell. The breadth of the claims is not deemed to be enabled because many of the chimeric proteins encompassed would not be able to initiate signaling in a host cell and it is deemed to constitute undue experimentation to determine which chimeric receptors encompassed would be have the required properties for the reasons set forth below. For brevity, the extracellular ligand binding domain will be referred to as the EC, the transmembrane domain will be referred to as the TM, and the cytoplasmic or intracellular domain will be referred to as the IC.

Stoddard et al. (Cold Spring Harb. Symp. Quant. Biol., 57:1-15, 1992) is cited as the most recent review article found by the Examiner discussing the mechanisms by which receptors generate transmembrane signaling to initiate intracellular events. Figure 1 illustrates four models. In (A) an EC ligand simultaneously binds to two individual EC subunits which then results in the association of the two IC subunits which then generates a new site for an intracellular signaling molecule to bind. No conformational change in the proteins is required. In (B) an EC ligand binds and causes a conformational change in both the EC and IC subunits. The receptor can be either a monomer or a dimer. In (C) two EC ligands bind to two EC subunits which results in dimerization of the monomers and a conformational change in both the EC and IC subunits. In (D) the IC of two receptors come in close enough proximity to associate and induce a conformational change in the IC. The conformational changes in (B)-(D) permit intracellular signaling to be initiated.

Models (A) and (D) require that the three dimensional structure of the EC, TM, and IC be suitable to associate correctly to initiate an intracellular signal. Models (B) and (C) require that the three dimensional structure of the EC, TM, and IC be suitable to generate the needed conformational change in the proteins in order for them to associate correctly to initiate an intracellular signal.

The claims are directed to chimeric proteins with disparate parts. The chimeric receptor comprises an extracellular binding domain of any surface membrane protein or any secreted protein where the ligand for said extracellular binding domain is a protein on the surface of a cell or a viral protein. The transmembrane domain can be artificial (synthetic) or from any transmembrane protein. The cytoplasmic domain may be from any protein which transduces a signal where the protein may not be naturally joined to an extracellular binding domain. It is not deemed to be so predictable that the resulting chimeric proteins will have the three dimensional structure necessary to generate an intracellular signal according to any of the mechanisms set forth above.

The specification exemplifies several different chimeric proteins where the IC is from the zeta chain; the TM is from the zeta chain, CD8α, or CD4; and the EC is from CD8α, CD4, or IgG/CD4 hybrids. There are examples of chimeric proteins where the EC is a single chain antibody and the TM and IC are both from the zeta chain or the TM is from CD4 and the IC is from the zeta chain. There are several examples of chimeric proteins where the EC is from CD4; the TM is from CD4, CD3γ,CD3δ, or CD3ε; and the IC is from CD3γ,CD3δ, or CD3ε. It does not appear from the specification that this last group of chimeric proteins was tested for ability to initiate any signal.

It is noted that the TM is never artificial (synthetic) and is always from either the EC or IC that is also present in the chimeric protein. Each of the TM used in the examples makes one pass through the membrane. However, many multiple pass TM and different one pass TM are known. (See for example Leucocyte Antigen Facts Book at page 22.) Thus, it could not have been predicted that substituting any of these multiple pass TM or one pass TM that were significantly different from the TM naturally attached to either the IC or EC in any of the exemplified embodiments would result in a chimeric protein capable of initiating a signal because the three dimensional conformation would not be expected to be suitable.

It is noted that CD8α and CD4 have some structural similarities in possessing variable domains in the EC that are Ig-like. (See for example Leucocyte Antigen Facts Book at pages 110 and 118.) However, many EC have very different structures and motifs. For example, the CD5 EC binds the B-cell membrane protein CD72. Its EC contains three cysteine rich domains. For example, CD21 (also known as CR2) is the Epstein-Barr virus receptor. Its EC is made up of complement control protein domains. (See for example Leucocyte Antigen Facts Book at pages 112 and 146.) Thus, it could not have been predicted that substituting any other dissimilar EC in any of the exemplified

embodiments would result in a chimeric protein capable of initiating a signal because the three dimensional conformation would not be expected to be suitable. It is also noted that many viral receptors such as cytomegalovirus (CMV) and herpes virus saimiri (HVS) are seven transmembrane receptors like G-protein linked receptors. They are very different from CD4 which binds HIV.

It is noted that the IC of the zeta chain, CD3γ, CD3δ, and CD3ϵ all contain similar motifs and possess potential phosphorylation sites thought to be involved in signal transduction. (See for example Leucocyte Antigen Facts Book at page 107.) The IC of CD4 can be phosphorylated and interacts with a tyrosine kinase. (See page 111.) The IC of CD8α binds to a tyrosine kinase. (See page 119.) Thus, some IC must interact with a particular tyrosine kinase to be phosphorylated themselves to initiate a signal whereas other IC must interact with particular proteins that must be phosphorylated to initiate a signal. It could not have been predicted that other IC would result in a chimeric protein capable of initiating a signal because the three dimensional conformation would not be expected to be suitable.

In addition, many IC have very different structures and generate signals in very different ways. G-protein coupled receptors have IC that activate messenger systems such as phospholipase C and adenylyl cyclase because binding a ligand to the EC causes the coupled G-protein to dissociate from the IC and thereby initiate a signal. (See for example G-Protein Linked Receptor Facts Book at page 361.) Thus, it could not have been predicted that substituting any G-protein coupled receptor IC in any of the exemplified embodiments would result in a chimeric protein capable of initiating a signal because the three dimensional conformation would not be expected to be suitable.

For those IC that do not generate the desired signal themselves but must act on other proteins or be acted upon themselves, the host cell must possess all of the needed surface membrane or intracellular components. Thus, it is noted that the claims encompass expression in any selected host cell; however, it does not appear that bacterial cells, yeast, or insect cells, for example, would possess these components.

In addition, the claims encompass chimeric proteins that have all of these disparate parts, e.g. EC from CD21, four-pass TM, and IC from G-protein coupled receptor. Such chimeric proteins would be even more unpredictable as to whether they would initiate a signal.

The specification does not establish any correlation or predictability between the chimeric proteins exemplified and the disparate chimeric proteins encompassed by the claims. It does not appear that the results from the exemplified embodiments can be reasonably extrapolated to support the breadth of the claims.

Claims 57-70 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57, line 10, recites "wherein said extracellular domain." It appears that this line should recite --wherein said extracellular binding domain-- for proper antecedent basis in the claim.

Claim 57 recites "wherein said extracellular domain and cytoplasmic domain are not naturally joined together, and said cytoplasmic domain is not naturally joined to an extracellular ligand binding domain." This phrase is either redundant or confusing. If the cytoplasmic domain is not naturally joined to an extracellular binding domain (e.g. is from a membrane bound protein that does not naturally possess an extracellular binding domain) then the extracellular and cytoplasmic domains would never be naturally joined together. Thus, these two limitations appear to be redundant unless applicant intended something else. Clarification is requested.

Claims 62-63 recite "extracellular domain." It appears that these claims should recite --extracellular binding domain-- for proper antecedent basis in claim 57. Likewise, claim 66 should recite --extracellular binding domain-- for antecedent basis in claim 64.

Claim 60 recites "heavy chain of an immunoglobulin, by itself or in conjunction with a light chain, or truncated portions thereof containing ligand binding activity." It is unclear whether this claim is directed to a single chimeric protein or a protein complex where the chimeric protein may be associated with additional light chain proteins. It appears from claim 61 that a single chimeric protein which is a single-chain antibody is intended. In addition, it is noted that claim 61 appears to broaden the subject matter of claim 60 by reciting "or portion thereof" without requiring the functional limitation of claim 60 ("containing ligand binding activity").

Claim 62 recites "is CD8" and claim 64 recites "is CD4." It appears that these claims should properly indicate that the extracellular domain is <u>from</u> CD4 and CD8. CD4 and CD8 are not

exclusively extracellular domains; they also contain transmembrane and cytoplasmic domains.

Claim 66 recites "is bound to a second protein to define a binding site." This is confusing because it appears to contradict the limitation in claim 57 that the EC binds the ligand on its own. It is unclear if the claim intends that a second binding site is defined.

Claims 69-70 recite "Class I or Class II MHC." It appears that this phrase is incomplete and that perhaps --Class I or Class II MHC antigen-- was intended.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen, whose telephone number is (703) 308-0666. The examiner can normally be reached on Monday-Thursday from 8:00 am to 5:30 pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Garnette D. Draper, can be reached on (703) 308-4232. The most convenient FAX telephone number for Art Unit 1812 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER
GROUP 18[illegible]